

Case Report

Clinical Features of Intestinal Behçet's Disease Associated with Myelodysplastic Syndrome and Trisomy 8

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Several studies have identified a relationship between myelodysplastic syndrome and Behçet's disease (BD), especially intestinal BD, and trisomy 8 appears to play an important role in these disorders. Despite this, only few case reports or series have been reported in gastroenterology, meaning that endoscopic findings and characteristics of intestinal BD have not been clarified yet. In this report, we describe three cases of intestinal BD associated with myelodysplastic syndrome and trisomy 8, and discuss the clinical features and problems of these disorders from a gastroenterology perspective.

Key words: Behçet's disease, trisomy 8, myelodysplastic syndrome

Behçet's disease (BD) is a chronic multisystem inflammatory disease first defined in the 1930s by Hulusi Behçet, and it is characterized by 4 clinical features: recurrent oral ulcers, genital ulcers, uveitis, and skin lesions [1]. Many other systems can be involved, such as the gastrointestinal tract, central nervous system, cardiovascular system, and the musculoskeletal system (in the form of arthritic joints).

Myelodysplastic syndrome (MDS) is a clonal hematologic disorder that easily converts to acute leukemia [2]. It is characterized by stem cell disorders, multilineage dysplasia, and pancytopenia due to ineffective hematopoiesis. Although BD and MDS are two different disease entities, several studies have identified a relationship between them, especially in the context of intestinal BD. Previous reports have also revealed that the chromosomal disorder trisomy 8 seems to play an important role in these disorders [3-11]. As most

of the BD and MDS cases or case series were reported by hematologists or rheumatologists, the clinical characteristics and endoscopic features of gastrointestinal involvement have not been adequately described from a gastroenterological perspective [5, 6].

Here we describe three cases of intestinal BD associated with MDS and trisomy 8. We illustrate the features of intestinal lesions, including those of the small intestines, as examined by colonoscopy and double-balloon endoscopy (DBE). We also discuss the clinical features and specific problems associated with these cases from the perspective of gastroenterologists.

Case Reports

Case 1. An 81-year-old Japanese man was referred to our hospital with frequent melena from multiple ulcers of the terminal ileum. DBE via the anal approach was performed, and multiple simple

ulcers with typical large oval shapes were detected in the deep ileum and terminal ileum (Fig. 1A). The histopathological examination of these ulcers showed nonspecific inflammation. He had relapsing oral aphthae, but no genital aphthae, or cutaneous, ophthalmologic, or neurologic lesions. HLA-B51 was examined, but negative. According to the above results, the patient was suspected of having intestinal BD. Several days after the DBE, massive bleeding occurred in the patient's terminal ileum, and hemostasis was achieved endoscopically. Treatment with per-oral steroids and continuous intravenous cyclosporin A infusion soon led to complete resolution of the melena.

Four weeks later, DBE revealed that the multiple ulcers had healed with minor scarring on the walls (Fig. 1B). However, moderate pancytopenia progressed throughout the clinical course. In particular, anemia continued despite complete resolution of the intestinal bleeding. A bone marrow examination revealed profound hypocellularity and the presence of trisomy 8. The patient was diagnosed with refractory anemia with ring sideroblasts (RARS). Immunosuppressive therapy was continued but the patient died from septic shock due to a urinary infection 7 months after being referred to our hospital.

Case 2. A 45-year-old Japanese man, who had been diagnosed with BD 5 years earlier based on the presence of aphthous oral ulcers and genital lesions with HLA-B51 positivity, was admitted to our hospital for abdominal pain and diarrhea. A colonoscopy was performed and revealed punched-out lesions around the ileocecal bulb that had created a fistula into the ileum (Fig. 2A). The patient was found to be pancytopenic and was simultaneously diagnosed with refractory anemia (RA) and trisomy 8. The International Prognostic Scoring System (IPSS) score was int-1.

Six months later, the patient developed excessive bleeding and localized peritonitis that could not be controlled by conservative therapy; therefore, ileocecal resection with ileostomy was performed (Fig. 2B). However, multiple ulcers compatible with intestinal BD recurred at the stoma site and in the residual ileum (Fig. 2C). He was considered to require resolution of both BD and MDS and a change in the behavior of the disease through resetting of the entire immune response by transplantation. Therefore, peripheral blood stem cell transplantation (PBSCT) was performed. Nevertheless, the patient died of

septic shock due to enteritis after 3 months.

Case 3. Two years prior to his referral to our hospital, the 64-year-old Japanese male patient had already been diagnosed with MDS (RA, IPSS int-1) with trisomy 8. Chronic anemia and thrombocytopenia continued, and immunosuppressive therapy was not effective. He was then referred to our hospital to undergo cord blood transplantation (CBT). Soon after admission, he developed frequent episodes of massive gastrointestinal (GI) bleeding that required an emergency colonoscopy, which revealed multiple simple ulcers—consistent with intestinal BD symptoms—in the ascending colon and terminal ileum (Fig. 3A). Several days later, multiple bleeding ulcers were revealed by DBE (Fig. 3B), but we could not endoscopically control the GI bleeding. Finally, the angiographic examination revealed extravasation, and the bleeding was stopped by transcatheter embolization. Although the patient had undergone CBT, he later died of septic shock due to pneumonia.

Discussion

We have presented the cases of 3 patients with intestinal BD associated with MDS and trisomy 8. All 3 patients had intestinal lesions and exhibited severe bleeding that required hemostasis.

The reported frequency of intestinal ulcers in BD is 3–16% [10]. However, Ahn *et al.* reported that the frequency of intestinal BD was significantly higher in patients with BD with bone marrow failure compared to those without bone marrow failure (61.5% vs. 13.6%) [3]. Handa *et al.* reviewed the data of 64 patients with BD and MDS, and they observed high frequencies of intestinal lesions (66%) and trisomy 8 (80%) but a low frequency of ocular lesions (13%). In particular, the data demonstrated that intestinal lesions were characteristic findings in BD associated with trisomy 8 and bone marrow failure, especially in MDS [12].

Several mechanisms have been demonstrated to explain the association between BD and MDS. Tada *et al.* indicated that trisomy 8 may lead to the development of intestinal ulcers in patients with MDS because the presence of trisomy 8 facilitates the production of inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interferon (IL)-6, and IL-1 β , which enhance neutrophil function and is a

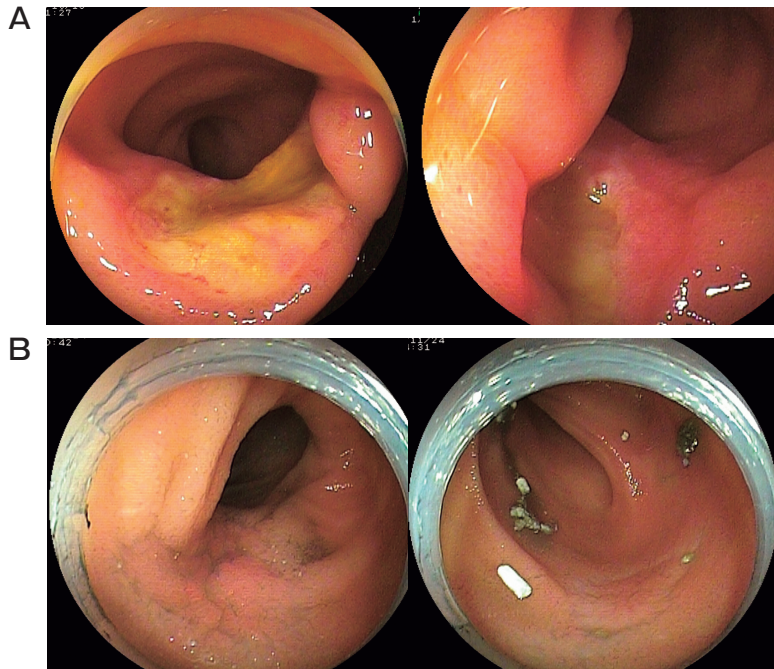


Fig. 1 Case 1, an 81-year-old man. (A) DBE showed multiple simple ulcers in the deep and terminal ileum. (B) Four weeks later, the multiple ulcers had healed and become scars.

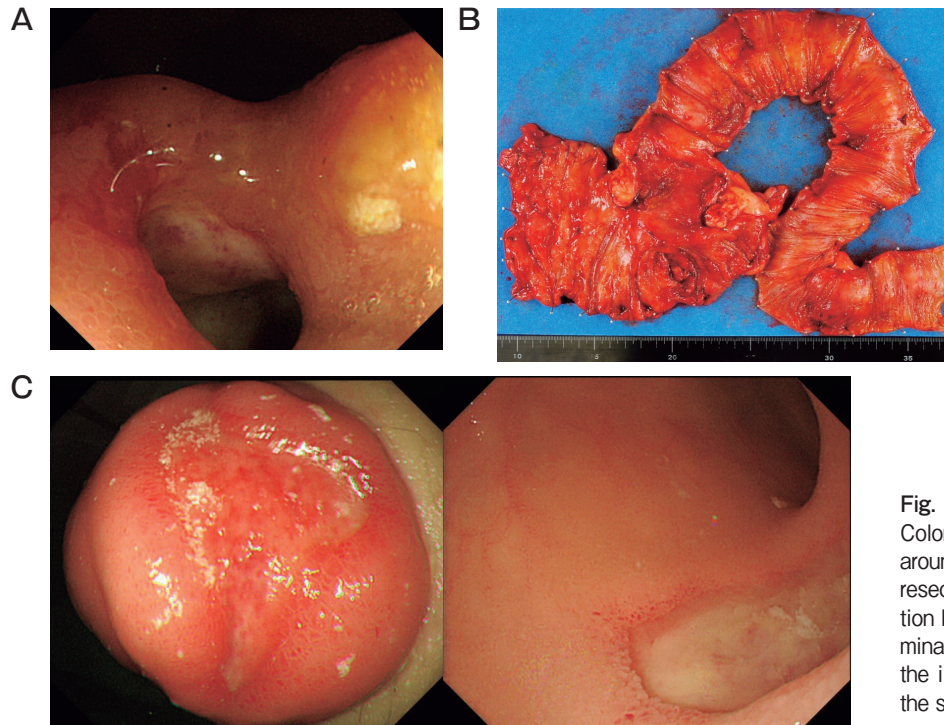


Fig. 2 Case 2, a 45-year-old man. (A) Colonoscopy revealed punched-out lesions around the ileocecal bulb. (B) Ileocecal resection with ileostomy revealed penetration between the ascending colon and terminal ileum, as well as multiple ulcers in the ileum. (C) Multiple ulcers recurred at the stoma site and in the residual ileum.

known risk factor for intestinal ulcers [4].

Interestingly, most of these cases were in East Asia, including Japan and Korea. Kawabata *et al.* suggested the importance of the regional, racial, and

environmental background of patients [7]. HLA-B51, one of the common allele types among Japanese, has been implicated in the higher occurrence of BD in Japanese. However, among the present 3 patients,

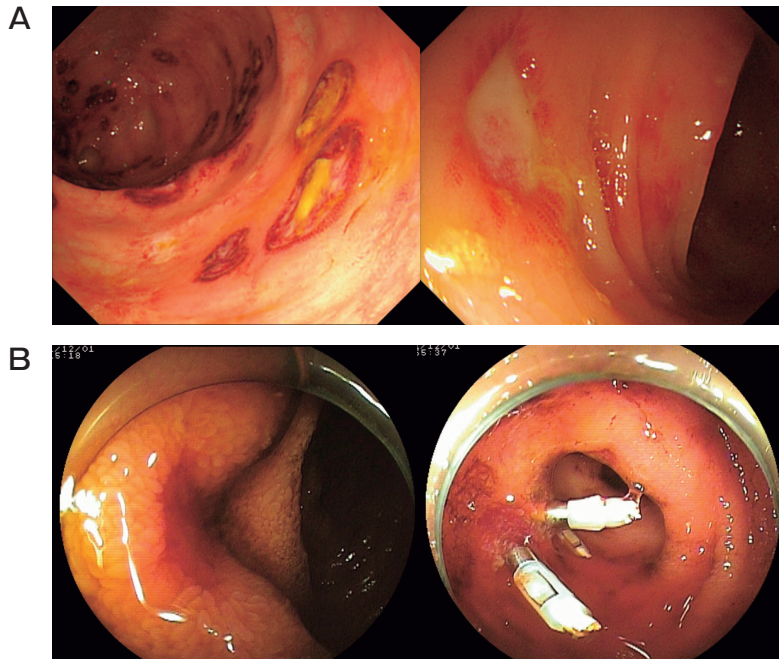


Fig. 3 Case 3, a 64-year-old man. (A) Colonoscopy revealed multiple simple ulcers in the ascending colon and terminal ileum. (B) Multiple bleeding ulcers were revealed by DBE.

only Case 2 had HLA-B51. Together with the previously reported cases [4, 6, 7, 9, 11], trisomy 8 seems to be a much more important risk factor for BD rather than HLA-B51 in patients with MDS with trisomy 8.

Lessons can be learned from our 3 patients regarding the management of intestinal BD in patients with MDS and trisomy 8. First, all 3 patients had intestinal lesions in the ileocecal region and deep in the small intestine. The ileocecal region and the ascending colon are known to be representative sites of gastrointestinal involvement in BD [11]. Small bowel involvement was recently detected in BD using capsule endoscopy and DBE [13]. We speculate that the small intestine is affected in many patients with BD given that enteroscopic examinations have been limited to only selected patients. We suggest that an examination of the small intestine with balloon endoscopy or capsule endoscopy should be performed in patients with intestinal BD, particularly in those with MDS and trisomy 8.

In addition, the onset of MDS and BD is not always simultaneous. In our Case 1, hematological abnormalities appeared several months after the intestinal symptoms, whereas BD had been diagnosed over 5 years earlier in Case 2. In Case 3, MDS had been diagnosed 2 years earlier and the patient was only seen during referral to receive CBT. Patients in whom the diagnosis of MDS precedes that of BD usu-

ally undergo a follow-up by a hematologist. Indeed, most of the cases in the literature were reported by hematologists. Gastroenterologists should therefore take into account the possibility of intestinal ulcers in patients with MDS and trisomy 8.

Case 2 was diagnosed with complete BD, and deep ileocecal ulcers were recognized as typical lesions of intestinal BD that cause localized peritonitis. However, after ileocecal resection, the lesions in all 3 patients were revealed to be relatively superficial and multiple in numbers.

There have been few reports of the characteristics of intestinal BD associated with MDS and trisomy 8. Hisamatsu *et al.* noted that the endoscopic findings of these lesions were different from those of typical intestinal BD (*i.e.*, those with no association with MDS or trisomy 8), and the findings showed giant, oval, punched-out ulcers at the ileocecum [14]. We speculate that multiple superficial ulcers are a characteristic of intestinal BD associated with MDS and trisomy 8. However, further investigation is required to clarify the similarities and differences of intestinal BD lesions in patients with and without MDS and trisomy 8.

Lastly, our 3 patients had poor prognoses. In Japan, the administration of 5-aminosalicylate, corticosteroids, and immunosuppressants is typically rec-

ommended as standard therapy for intestinal BD [15]. Additionally, effective anti-TNF α monoclonal antibody therapy (infliximab and adalimumab) has been developed [16]. Kimura *et al.* recently reported the usefulness of adalimumab in the treatment of a case of intestinal BD with trisomy 8 MDS [17]. Whereas several reports suggested that infliximab might not be effective [5, 11]. We still think that the use of anti-TNF α monoclonal antibody therapy is controversial, because difficult-to-control infections could occur in association with MDS and trisomy 8 as described in our three cases. Tanaka *et al.* reported the effectiveness of azacitidine therapy [11], but there was also insufficient evidence. There have also been a few case reports and systemic reviews of the successful treatment of intestinal BD with trisomy 8 MDS by bone marrow transplantation [9, 18], which, we believe, is the best therapy at present, particularly for younger patients. However, Soysal *et al.* warned that potentially fatal adverse events and complications of bone marrow transplantation therapy must be taken into consideration [18]. Gastroenterologists should pay particular attention to any intestinal bleeding, making the evaluation of the entire gastrointestinal tract vital in such patients.

In conclusion, we have described 3 cases of intestinal BD associated with MDS and trisomy 8. The diagnosis and treatment of such patients may be complicated, but we believe that an improved understanding of the complex disease and collaborative efforts by hematologists, rheumatologists, and gastroenterologists can lead to improved care and reduce adverse outcomes.

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